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Multicenter phase II study of trabectedin in patients with metastatic castration-resistant prostate cancer

M. D. Michaelson[1]*, J. Bellmunt[2], G. R. Hudes[3], S. Goel[4], R. J. Lee[1], P. W. Kantoff[5], C. A. Stein[4], P. Lardelli[6], I. Pardos[6], C. Kahatt[6], A. Nieto[6], M. Cullell-Young[6], N. L. Lewis[3] & M. R. Smith[1]

[1]Massachusetts General Hospital Cancer Center, Boston, USA; [2]Medical Oncology Service, Hospital del Mar, Barcelona, Spain; [3]Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia; [4]Department of Oncology, Montefiore-Einstein Cancer Center, Bronx; [5]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA; [6]Clinical R&D, PharmaMar, Colmenar Viejo, Madrid, Spain

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Background: This multicenter phase II trial evaluated the efficacy and safety of trabectedin in metastatic castration-resistant prostate cancer (CRPC).

Patients and methods: Two schedules were evaluated in three cohorts: weekly as 3-h i.v. infusion at 0.58 mg/m^2 for 3 out of 4 weeks (Cohort A, $n = 33$), and every 3 weeks (q3wk) as 24-h infusion at 1.5 mg/m^2 (Cohort B1, $n = 5$) and 1.2 mg/m^2 (Cohort B2, $n = 20$). The primary end point was prostate-specific antigen (PSA) response; secondary end points included safety, tolerability and time to progression (TTP).

Results: Trabectedin resulted in PSA declines ≥50% in 12.5% (Cohort A) and 10.5% (Cohort B2) of patients. Among men pretreated with taxane-based chemotherapy, PSA response was 13.6% (Cohort A) and 15.4% (Cohort B2). PSA responses lasted 4.1–8.6 months, and median TTP was 1.5 months (Cohort A) and 1.9 months (Cohort B2). The dose of 1.5 mg/m^2 (approved for soft tissue sarcoma) given as 24-h infusion q3wk was not tolerable in these patients. At 1.2 mg/m^2 q3wk and 0.58 mg/m^2 weekly, the most common adverse events were nausea, fatigue and transient neutropenia and transaminase increase.

Conclusions: Two different trabectedin schedules showed modest activity in metastatic CRPC. Further studies may require identification of predictive factors of response in prostate cancer.

Key words: chemotherapy, docetaxel, prostate cancer, second-line, trabectedin

introduction

Prostate cancer is a leading cause of cancer mortality, estimated to be responsible for ∼32 000 deaths in 2010 in the United States and 94 000 deaths in the European Union (EU) [1, 2]. Androgen deprivation therapy (ADT) is the mainstay of treatment for recurrent prostate cancer, but ultimately, most patients develop resistance to treatment. Following progression to castration-resistant prostate cancer (CRPC), men are at high risk for developing metastatic disease and life-threatening complications. The standard of care for initial treatment of metastatic CRPC is docetaxel-based chemotherapy, with a modest survival benefit compared with mitoxantrone plus prednisone. The novel semisynthetic taxane cabazitaxel recently gained regulatory approval for treatment of docetaxel-resistant CRPC [3]. Immunotherapy with sipuleucel-T is associated with a survival benefit and has been approved in the United States for CRPC [4]. Abiraterone acetate is the first hormonal agent approved in the United States for metastatic CRPC following docetaxel-based chemotherapy [5, 6]. Since the benefits of these treatments are transient, additional agents are urgently needed in this population.

Trabectedin is a novel marine-derived antineoplastic agent initially isolated from the tunicate *Ecteinascidia turbinata* and currently produced synthetically. Trabectedin is a DNA-binding cytotoxic agent with activity in preclinical models of taxane-resistant prostate cancer [7, 8]. It is currently approved as single agent in the EU for treatment of soft tissue sarcoma and combined with pegylated liposomal doxorubicin for treatment of relapsed platinum-sensitive ovarian cancer. In this phase II trial, single-agent trabectedin was administered to men with metastatic CRPC. A weekly schedule was given in the initial cohort (Cohort A). When the every-3-week (q3wk) schedule was noted to be more effective in other malignancies [9], another cohort (Cohort B) was treated with a 24-h infusion q3wk. The efficacy and safety in each cohort are reported here.

materials and methods

Patients were recruited from four sites in the United States ($n = 3$) and Spain ($n = 1$). The study protocol was approved by the institutional review board of each center and was conducted in accordance with the Declaration of Helsinki,

Correspondence to: Dr M. D. Michaelson, Massachusetts General Hospital Cancer Center, 55 Fruit Street, Yawkey 7E, Boston, MA 02114, USA. Tel: +1-617-726-1594; Fax: +1-617-726-3440; E-mail: dmichaelson1@partners.org

Good Clinical Practice guidelines and local regulations. Signed informed consent was obtained from all patients before any study-specific procedure.

eligibility criteria

Eligibility criteria included histologically confirmed adenocarcinoma of the prostate; radiologically documented metastatic disease; surgical or ongoing chemical castration; prostate-specific antigen (PSA) >5 ng/ml; castration-resistant disease (defined by detectable rising PSA in two consecutive measurements at least 1 week apart, with a minimum increment of at least 5 ng/ml above the nadir) [10]; no more than one prior chemotherapy regimen (Cohort A) or previous treatment with one docetaxel-based chemotherapy regimen (Cohorts B1 and B2); Eastern Cooperative Oncology Group performance status score of zero to two and adequate hematologic, renal, and hepatic function. The total alkaline phosphatase (AP) had to be $<1.5 \times$ upper limit of normal (ULN); if AP $\geq 1.5 \times$ ULN, men were still eligible if the AP liver fraction or the 5′-nucleotidase or gamma glutamyltransferase (GGT) were within normal limits.

Exclusion criteria also included small-cell carcinoma of the prostate, extensive external-beam radiation therapy or radionuclide therapy within 6 weeks, chemotherapy or any radiation therapy within 4 weeks and other uncontrolled medical conditions.

study treatment

Trabectedin (PharmaMar, Colmenar Viejo, Madrid, Spain) was administered through a central i.v. line either by 3-h infusion of 0.58 mg/m^2 weekly on Days 1, 8 and 15 in 4-week cycles (Cohort A) or by 24-h infusion q3wk at 1.5 mg/m^2 (Cohort B1) or 1.2 mg/m^2 (Cohort B2). A treatment cycle was 4 weeks in Cohort A and 3 weeks in Cohort B. Dexamethasone prophylaxis (10 mg i.v. for Cohort A and 20 mg for Cohort B) was administered 30 min before trabectedin, and 5-HT3 blockers were recommended. Prophylactic use of hematopoietic colony-stimulating factors was not permitted in the first cycle; but therapeutic use of granulocyte colony-stimulating factor or granulocyte/macrophage colony-stimulating factor for serious neutropenic complications was permitted at the investigator's discretion. Patients were permitted to receive ADT and bisphosphonates. No other chemotherapy or experimental antineoplastic therapies were permitted. Trabectedin was administered until progressive disease (serially rising PSA values, worsening symptoms or new radiographic findings) or intolerance.

A maximum of two dose reductions were allowed for the following adverse events (AEs): febrile neutropenia, grade 4 neutropenia lasting >5 days, grade 4 thrombocytopenia, persistent grade 3/4 transaminase elevation, increased AP of hepatic origin, increased total bilirubin of any grade, intractable grade 3/4 nausea/vomiting, or any other grade 3/4 non-hematological toxicity.

efficacy assessment

Efficacy was assessed monthly by evaluating PSA response according to the National Cancer Institute PSA Working Group criteria [10]. Patients with at least one PSA determination after treatment onset were assessable for efficacy. PSA response was defined as decline in serum PSA ≥50% compared with pretreatment levels on two serial measurements carried out at least 28 days apart. Based on recommendations of the Prostate Cancer Clinical Trials Working Group [11], the maximum decline in PSA at any point after treatment was reported in a waterfall plot. Secondary end points included duration of PSA response and time to progression (TTP), calculated from the starting date of trabectedin treatment to the date of first documentation of progressive disease. Radiological response rate was evaluated according to the World Health Organisation (WHO) criteria [12].

safety assessment

All patients who received at least one trabectedin infusion were assessable for safety. AEs were graded according to the National Cancer Institute—Common Toxicity Criteria (NCI–CTC), v. 2.0. Safety evaluations occurred throughout the study and until 30 days after the final study treatment, and all patients were followed until recovery from any drug-related AE.

pharmacogenomic analysis

Paraffin-embedded tumor tissue samples were collected from consenting patients. XPG, ERCC1 and BRCA1 RNA expression was assessed by quantitative reverse transcription–PCR. The presence of TMPRSS2-ERG chromosomal translocation was analyzed by PCR using specific ETS primers.

statistical methods

sample size. Sample size was based on the primary end point (PSA response rate). In Cohort A, a Simon's two-stage design [13] was adopted to test the null hypothesis of PSA response rate of 5% versus the alternative hypothesis of PSA response rate of 25%. In the first stage, 17 patients were enrolled (15 assessable for response). If fewer than two patients achieved PSA response, the study would be terminated due to lack of efficacy. If two or more patients achieved PSA response, enrollment would proceed to the expected total of 33 patients (30 eligible). Trabectedin therapy would be declared promising if four or more men achieved PSA response. Using this design, there was a 9.6% probability of rejecting a promising treatment (β) and a 4.5% probability of accepting an uninteresting treatment (α).

After the initial cohort of 33 men was completed, a protocol amendment established a second cohort (Cohort B) with a similar two-stage design. In Cohort B1, five patients were given trabectedin at 1.5 mg/m^2 q3wk. After a safety review, treatment was resumed at a lower starting dose (1.2 mg/m^2). In Cohort B2, a single-stage design included 16 patients previously treated with one docetaxel-based regimen, who received trabectedin 1.2 mg/m^2 q3wk. At the end of recruitment, 4 patients were already under screening and therefore 20 patients were enrolled in Cohort B2. If three or more responses had been observed, enrollment would have proceeded to 33 patients. With this design, there was a <20% probability ($\beta = 0.197$) of rejecting a promising treatment (25% or higher response rate) and a <5% probability ($\alpha = 0.043$) of accepting a non-promising treatment (5% or lower response rate) for further evaluation.

statistical analyses. No formal comparisons were done between Cohorts A and B. The cut-off date for data analysis was the last clinical follow-up date: 10 April 2007 (Cohort A), 14 December 2007 (Cohort B1) and 10 November 2008 (Cohort B2).

Two populations were defined in this study. The all-treated population included patients who received at least one trabectedin dose. This population was analyzed for safety and, as supportive data, for the efficacy analysis. The primary efficacy analysis was based on the population of men with at least one PSA determination after at least one trabectedin dose.

The PSA response rate was calculated with its binomial exact estimator and confidence intervals at 95% (95% CI). PSA outcomes were reported at these post-treatment intervals: 3, 6, 12, 18 and 24 months. Median TTP was analyzed by the Kaplan–Meier method.

results

patient characteristics

Fifty-eight men were treated: 33 in Cohort A, 5 in Cohort B1 and 20 in Cohort B2 (Figure 1). Demographic and baseline characteristics are shown in Table 1. All men had metastatic disease, with bone and lymph nodes as the most common sites of disease. Most were previously treated with radical prostatectomy or prostate radiation therapy. All men were treated with primary ADT, most had received secondary

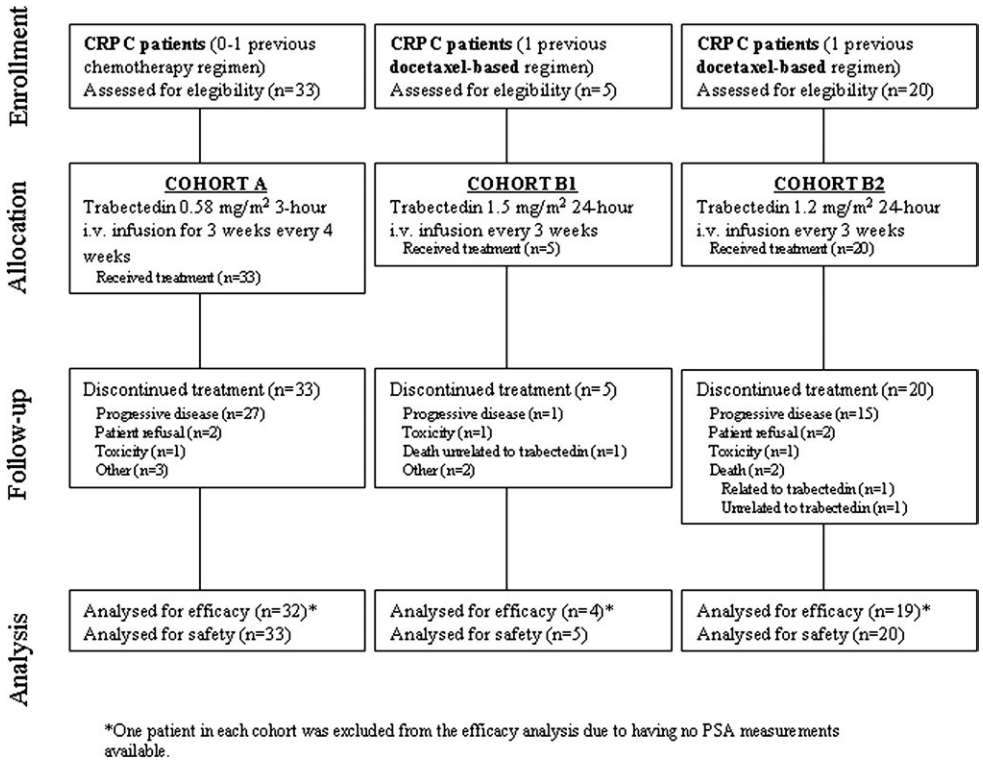

Figure 1. Study flow chart. CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen.

hormone therapy (median of two prior hormone therapies, range, 1–5), and most had received prior chemotherapy. Median time from last docetaxel to study entry was 1.9 months in Cohort A and 4.7 months in Cohort B2.

treatment and dosing

A total of 110 trabectedin cycles were administered to 33 patients in Cohort A, with a median of two cycles per patient (range, 1–19) and a median relative dose intensity of 88.2%. Most patients (n = 27, 81.8%) discontinued due to disease progression (Figure 1).

The five patients in Cohort B1 received 11 trabectedin cycles, with a median of two cycles per patient (range, 1–4) and a median relative dose intensity of 82.3%. This cohort was closed due to safety concerns.

Twenty patients in Cohort B2 received 105 trabectedin cycles, with a median of four cycles per patient (range, 1–15) and a median relative dose intensity of 93.4%. Most patients (n = 15, 75.0%) discontinued due to disease progression.

efficacy

One patient per cohort was excluded from the primary efficacy analysis due to absence of post-treatment PSA measurements.

cohort A. Confirmed PSA decline ≥50% occurred in 4 of 32 (12.5%) assessable men. Three of these 4 patients were resistant to prior docetaxel, for a response rate of 13.6% among the 22 taxane-resistant patients in this cohort (Table 2). One additional patient had an unconfirmed PSA decline ≥50%. The duration of PSA response ranged from 4.5 to 6.5 months. The median TTP was 1.5 months (95% CI 0.9–1.8 months).

Maximal PSA changes as percent of baseline PSA are shown in Figure 2A. Nine of 32 men (31.3%) manifested any PSA decrease, and 7 (21.9%) had PSA decrease ≥30%. By radiographic criteria (WHO), 15 patients (45.5%) had disease stabilization (Table 3), 7 of them lasting >3months.

cohort B1. A high rate of serious AEs was observed in Cohort B1 (1.5 mg/m^2 by 24-h infusion q3wk) and recruitment was stopped. This group was not considered assessable for response.

cohort B2. Confirmed PSA decline ≥50% occurred in 2 of 19 (10.5%) assessable patients. Following the study design criteria, this cohort did not enter the second enrollment stage. Two additional patients (10.5%) had an unconfirmed PSA decline ≥50%. The two confirmed responses lasted 4.1 and 8.6 months. The median TTP was 1.9 months (95% CI 1.2–3.5 months). Maximal PSA changes as percent of baseline are shown in Figure 2B. Nine of 19 men (47.4%) manifested any degree of PSA decrease, and 6 (31.6%) had PSA decrease ≥30%. Radiographic evaluation noted one unconfirmed partial response and 9 (45%) disease stabilizations (Table 3).

safety

Four of five men in Cohort B1 experienced treatment-related serious AEs. These included febrile neutropenia, myocardial infarction, pulmonary edema, diarrhea, nausea, vomiting, fatigue, increased lipase, dyspnea and venous thrombosis (n = 1 each). Most were grade 3, with one case of grade 4 myocardial infarction. Hematological abnormalities were also common, including grade 3/4 leukopenia, grade 3/4 neutropenia, grade 3 lymphopenia (n = 4 each) and grade 3/4 thrombocytopenia (n = 3). Two

Table 1. Demographic and baseline characteristics

Characteristic	Cohort A ($N = 33$) n (%)	Cohort B1 ($N = 5$) n (%)	Cohort B2 ($N = 20$) n (%)
Age (years) (range)	68 (43–83)	67 (49–78)	68 (53–81)
ECOG PS			
0–1	30 (90.9)	5 (100.0)	19 (95.0)
2	3 (9.1)	–	1 (5.0)
Hemoglobin			
≥10 g/dl	29 (87.9)	5 (100.0)	17 (85.0)
<10 g/dl	4 (12.1)	–	3 (15.0)
Gleason score			
≤7	8 (24.2)	2 (40.0)	5 (25.0)
8–10	22 (66.7)	3 (60.0)	13 (65.0)
Unknown	3 (9.1)	–	2 (10.0)
Median baseline PSA (ng/ml) (range)	117 (15–2280)	212 (148–603)	128 (13–2113)
Sites of metastatic disease			
Bone	26 (78.8)	4 (80.0)	16 (80.0)
Lymph nodes	22 (66.7)	4 (80.0)	11 (55.0)
Liver	3 (9.1)	–	2 (10.0)
Lung	3 (9.1)	1 (20.0)	4 (20.0)
Other[a]	7 (21.2)	4 (80.0)	3 (15.0)
Previous therapy			
Prostatectomy	20 (60.6)	–	6 (30.0)
Radiotherapy[b]	17 (51.5)	2 (40.0)	6 (30.0)
Chemotherapy	26 (78.8)	5 (100.0)	20 (100.0)
Median number of previous chemotherapy regimens (range)	1 (0–2)	1 (1–1)	1 (1–4)
Months since l ast docetaxel (range)	1.9 (0.9–44.1)	4.2 (1.8–12.5)	4.7 (1.1–32.2)

[a]Cohort A: adrenal, bladder, pancreas, pleura, prostate, soft tissue and stomach ($n = 1$ each). Cohort B1: soft tissue ($n = 2$), bladder and pancreas ($n = 1$ each). Cohort B2: pleura ($n = 2$) and soft tissue ($n = 1$).
[b]Prostate and/or pelvis.
ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen.

Table 2. PSA response in patients with castration-resistant prostate cancer treated with trabectedin

	Efficacy population[a] n (%)	Taxane-resistant patients[b] n (%)
Cohort A		
PSA response	4 (12.5)	3 (13.6)
Unconfirmed PSA response[c]	1 (3.1)	1 (4.5)
SD	12 (37.5)	9 (40.9)
PD	15 (46.9)	9 (40.9)
NE	–	–
Total	32 (100.0)	22 (100.0)
Cohort B2		
PSA response	2 (10.5)	2 (15.4)
Unconfirmed PSA response[c]	2 (10.5)	2 (15.4)
SD	12 (63.2)	7 (53.8)
PD	3 (15.8)	1 (7.7)
NE	–	1 (7.7)[d]
Total	19 (100.0)	13 (100.0)

PSA response = decline in serum PSA ≥50% compared with pretreatment levels on two serial measurements done at least 28 days apart. Recruitment in Cohort B1 was stopped due to safety reasons, with no PSA responses or PSA stabilizations longer than 3 months.
[a]Two patients had no PSA measurements during treatment and were excluded from the primary analysis of efficacy.
[b]Patients with progression during or within 60 days after stopping taxane chemotherapy.
[c]PSA decrease was not confirmed in a second determination done at least 28 days later.
[d]Patients excluded from the analysis due to having no PSA measurements.
NE, not evaluable; PD, progressive disease; PSA, prostate-specific antigen; SD, stable disease (PSA stabilization).

patients were withdrawn due to AEs: grade 4 myocardial infarction and grade 3 lipase elevation ($n = 1$ each). Based on these events, no additional patients were treated in this cohort.

Detailed safety data for Cohorts A and B2 are provided in Table 4. Most treatment-related AEs were mild/moderate, with nausea, vomiting and fatigue as the most common. Three patients in each cohort had grade 3/4 treatment-related AEs: fatigue ($n = 3$), pneumonia, neutropenic sepsis, vomiting, weakness, bone pain and tachycardia ($n = 1$ each). In Cohort A, the most common grade 3 hematological abnormality was lymphopenia. One patient in this cohort had grade 3 neutropenia, leukopenia and thrombocytopenia and was withdrawn after two cycles due to disease-related fatigue. No cases of febrile neutropenia occurred. The most common grade 3/4 biochemical abnormality was serum AP elevation ($n = 7$), although six of these patients had baseline grade ≥2 elevation. Transient grade 3/4 transaminase and GGT increases were observed in only one patient. Two patients in Cohort A were withdrawn due to AEs (tachycardia and fatigue, one each). In Cohort B2, hematological abnormalities were mostly grade 3 and most cases of severe neutropenia returned to grade <2 within 15 days. Grade 3/4 AP increase occurred in four men, of whom two had baseline grade ≥2 elevation. One patient in this cohort died of treatment-related toxicity event (neutropenic sepsis). Another patient was withdrawn due to treatment-related grade 2 pancytopenia.

pharmacogenomic analysis

Samples were obtained from 29 patients. No differences in response to trabectedin were found according to BRCA1 or XPG RNA levels. A trend to a better outcome was observed in patients expressing high ERCC1 RNA levels and in patients negative for TMPRSS2-ERG translocation, but neither reached significance ($P = 0.0577$ and $P = 0.1927$, respectively).

discussion

This phase II trial evaluated the efficacy and safety of single-agent trabectedin in men with histologically confirmed metastatic CRPC progressing after first- or second-line chemotherapy. Two schedules were evaluated in three cohorts: weekly (Cohort A) and q3wk (Cohorts B1 and B2). Two doses

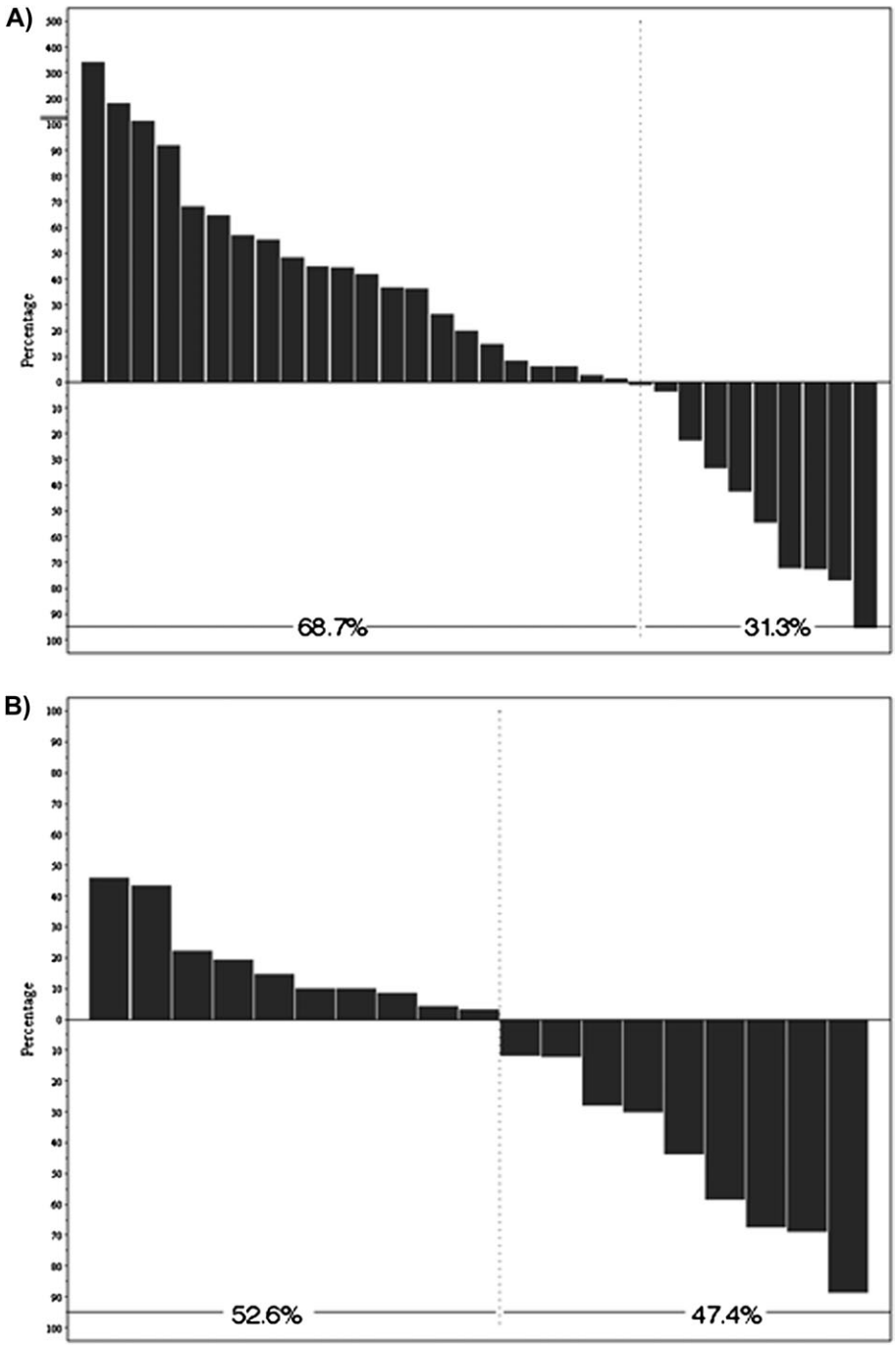

Figure 2. Waterfall plot showing maximal prostate-specific antigen (PSA) changes as a percent of baseline. (A) Cohort A. (B) Cohort B2. Data from Cohort B1 not shown due to small sample size. For each patient, the minimum among all post-baseline PSA values was identified and expressed as a percent change from baseline. For patients with a post-baseline nadir, plotted values are maximum PSA decrease.

were evaluated for the q3wk schedule: 1.5 mg/m^2 (Cohort B1) and 1.2 mg/m^2 (Cohort B2).

In Cohort A (0.58 mg/m^2 weekly), CRPC patients treated with no more than one previous chemotherapy regimen could be enrolled. Although prior taxane treatment was not mandatory in this cohort, most patients (73%) had received prior docetaxel and another 6% had received prior paclitaxel. In this cohort, four patients (12.5%) achieved a confirmed PSA decline of ≥50% and each of these patients had radiographic stable disease. In the subset of 22 taxane-resistant patients, 7 (21.9%) had confirmed PSA decrease ≥30% and 3 (13.6%) had confirmed PSA decline of ≥50%. These results prompted an amendment to expand recruitment of patients treated with one prior docetaxel-containing regimen (Cohort B) and to change the schedule to q3wk based on efficacy data with trabectedin in other tumors [9, 14]. The rate of serious AEs in the first five patients in the new cohort was unacceptably high and the starting dose changed from 1.5 to 1.2 mg/m^2. As a result, no

efficacy conclusions can be drawn from patients treated at 1.5 mg/m^2. Trabectedin at 1.2 mg/m^2 q3wk resulted in confirmed PSA decline of ≥50% in 2 (10.5%) of 20 men previously treated with docetaxel-based regimens. These two patients also had radiographic disease stabilization. Two additional unconfirmed PSA responses in docetaxel-resistant patients were observed, one of whom had a radiographic partial response.

The safety profile was similar in Cohorts A and B2. The most common AEs were nausea, fatigue and transient laboratory abnormalities (increased AP and transaminases). Grade 3 neutropenia occurred in 11% of 53 patients treated in both cohorts; no febrile neutropenia was observed. Thrombocytopenia and nausea were more frequent in Cohort B2 than in Cohort A.

The overall safety profile was similar to that seen in trials using these schedules in sarcoma and breast carcinoma [9, 15]. Laboratory abnormalities were transient, decreased in frequency over cycles, were not cumulative and were readily managed with dose adjustments. The rate of treatment-related serious AEs in this study (12.1%) was consistent with that reported in phase II trials with the weekly regimen (10% in a pooled analysis of 304 treated patients; unpublished data).

At the time this clinical trial was initiated, no standard of care was available for progressive CRPC after first-line docetaxel-based chemotherapy, and novel second-line options were urgently needed [16]. More recently, new active agents have increased overall survival in this population. A semisynthetic taxane, cabazitaxel, has achieved a 30% reduction of the risk of death and improved overall survival compared with mitoxantrone [3]. Another novel therapeutic, the CYP17 inhibitor abiraterone acetate, prolongs overall survival in men with metastatic CRPC progressing after docetaxel chemotherapy [17] and is now approved in the United States. Other novel hormonal agents are also in late-stage investigation and may soon further expand the therapeutic armamentarium for advanced prostate cancer.

Translational pharmacogenomic research in other solid tumors has identified a set of genes that correlate with *in vitro* response to pharmacological concentrations of trabectedin [18, 19]. Clinical response to trabectedin may be modulated by several DNA repair genes in a unique pattern [18, 20]. Tumor sensitivity to trabectedin may be related to altered expression of some DNA repair genes (e.g. *BRCA1* or *BRCA2*) [21]. In this study, a trend to a better response to trabectedin was found in patients expressing high RNA levels of the DNA repair gene *ERCC1*, but the number of analyzed patients was too small to draw definitive conclusions. Further translational studies could help characterize a subset of prostate cancer patients with a higher probability of benefit from trabectedin treatment.

Table 3. Radiological response (according to World Health Organisation criteria)

	Cohort A (0.58 mg/m^2, weekly) *n* (%)	Cohort B2 (1.2 mg/m^2, q3wk) *n* (%)
PRnc	–	1 (5.0)
SD	15 (45.5)	9 (45.0)
PD	13 (39.4)	7 (35.0)
NE	5 (15.2)	3 (15.0)
Total	33 (100.0)	20 (100.0)

NE, nonevaluable; PD, progressive disease; PRnc, non-confirmed partial response; SD, stable disease; q3wk, every 3 weeks.

Table 4. Worst grade trabectedin-related adverse events (≥10% of patients)

Adverse event	Cohort A (trabectedin 0.58 mg/m^2 3-h weekly for 3 weeks every 4 weeks) *N* = 33			Cohort B2 (trabectedin 1.2 mg/m^2 24-h every 3 weeks) *N* = 20		
	Grade 1/2 *n* (%)	Grade 3/4 *n* (%)	Total *n* (%)	Grade 1/2 *n* (%)	Grade 3/4 *n* (%)	Total *n* (%)
Anorexia	8 (24)	–	8 (24)	6 (30)	–	6 (30)
AP increase	17 (52)	7 (21)	24 (73)	8 (40)	4 (20)	12 (60)
ALT increase	23 (70)	1 (3)	24 (73)	12 (60)	4 (20)	16 (80)
AST increase	22 (67)	1 (3)	23 (70)	12 (60)	3 (15)	15 (75)
Constipation	5 (15)	–	5 (15)	3 (15)	–	3 (15)
Fatigue	13 (39)	2 (6)	15 (45)	7 (35)	1 (5)	8 (40)
GGT increase	18 (60)	1 (3)	19 (63)	15 (75)	2 (10)	17 (85)
Hypoesthesia	4 (12)	–	4 (12)	–	–	–
Insomnia	5 (15)	–	5 (15)	–	–	–
Leukopenia	21 (64)	1 (3)	22 (67)	11 (55)	5 (25)	16 (80)
Lymphopenia	18 (55)	3 (9)	21 (64)	7 (35)	8 (40)	15 (75)
Nausea	20 (61)	–	20 (61)	11 (55)	–	11 (55)
Neutropenia	11 (33)	1 (3)	12 (36)	8 (40)	5 (25)	13 (65)
Thrombocytopenia	3 (9)	1 (3)	4 (12)	5 (25)	2 (10)	7 (35)
Vomiting	7 (21)	–	7 (21)	8 (40)	1 (5)	9 (45)

Data from Cohort B1 not shown due to the small sample size. Data for GGT increase were available from 30 patients in Cohort A and 20 patients in Cohort B2.

AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase.

In conclusion, trabectedin administered weekly or q3wk exhibits modest antitumor activity in men with metastatic CRPC either before or following docetaxel-based chemotherapy. Future studies in prostate cancer should include molecular characterization of tumors that might have enhanced sensitivity to trabectedin.

funding

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disclosures

PL, IP, CK, AN and MC-Y are PharmaMar employees. GRH, PWK, CAS, NLL and MRS declare no conflicts of interest.

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